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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/815,937	ALLEN ET AL.	
	Examiner	Art Unit	
	Celine X Qian Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-70 and 72-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-70 and 72-76* is/are rejected.

7)☒ Claim(s) *76* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 63-70 and 72-76 are pending in the application.

This Office Action is in response to the Amendment filed on 11/12/04.

Response to Amendment

Claims 63-70 and newly added claims 72-76 stand rejected under 35 U.S.C. 101/112 1st paragraph for reasons set forth of the record mailed on 8/12/04 and further discussed below.

Claims 63-70 and 72-75 are rejected under 35 U.S.C. 112 1st paragraph for reason discussed below.

Claim 70 is rejected under 35 U.S.C.112 2nd paragraph for reasons discussed below.

Claim 76 is objected for reasons discussed below.

Response to Arguments

Claim Rejections - 35 USC § 101

Claims 63-70 and newly added claims 72-76 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility.

Claims 63-70 and newly added claims 72-76 also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In response to this rejection, Applicant argues that the examiner's conclusion regarding the ability of the skilled artisan to use the claimed invention is not consistent with the rules regarding the utility of an invention because the claimed invention has a well-established utility

and practical purpose. Applicant assert that the skilled in the art would immediately appreciate how to use a knockout mouse because any knockout mouse has the inherent and well-established utility of defining the function and role of the disrupted gene regardless of specific phenotypes, characterizations or properties of the knockout mouse. Applicant further cites a passage at NIH website which indicate that knockout mice represent a critical tool in studying gene function. Applicant asserts that the knockout mouse have a clear, specific and unquestionable utility as with gas chromatographs, screening assays and nucleotide sequence techniques as taught by MPEP 2107.01,I. Furthermore, Applicant asserts that the newly amended claims drawn to transgenic mouse comprising null-reporter alleles "is an indispensable starting point for studying the function of every gene"(Austin et al., 2004), "is an invaluable tool for investigating gene function on a genomic scale"(Molecular biology of Cell, Albert, 4th ed., Garland Science (2002), "is a powerful tool to investigate directly the importance and function of the gene" (Genes VII, Oxford university 2000), "offers a powerful approach to study gene function in a mammalian organism" (Joyner, Gene targeting: A practical approach, Oxford university press 2000), "has revolutionized our ability to study gene function in cell culture and *in vivo*" (Matise et al., Joyner, Gene targeting: A practical approach, Oxford university press 2000), and "provide an important means for understanding gene function." (Crawley, What's wrong with my mouse behavioral phenotype of transgenic and knockout mice, Wiley-Liss 2000). Moreover, Applicants indicates that the claimed invention is purchased by two largest pharmaceutical companies, thus such commercial acceptance more than satisfied the practical utility requirement of 101 and 112 1st paragraph. Further, Applicant asserts that the examiner has stated that one of ordinary artisan would have been motivated to produce the GPCR knockout mouse to study the function of

GPCR in the 103 (a) rejection previously, and such statement is an admission that the skilled artisan would know how to use the claimed invention to determine the function of a gene. Applicant thus concludes that the claimed invention has a well-established utility. Applicant also asserts that the claimed invention is useful for a particular purpose, to study the role of GPCR in anxiety and immunological disorder in light of the observed phenotypes. Furthermore, Applicant argues that the utility of the claimed inventions does not depend on a correlation between the disclosed phenotype and a disease in human for the enablement of the claimed invention according to *In re Brana*. Applicant asserts that usefulness in patent law necessarily includes the expectation of further research and development according to *In re Brana*. Moreover, Applicant argues since the null GPCR gene results in lymphocytic infiltration, a GPCR agonist will have value because it can control immune response. Lastly, Applicant argues that the claimed mouse can be used to study gene expression. Applicant thus concludes that the claimed invention has credible, substantial and specific utility.

These arguments have been fully considered but deemed unpersuasive. The reasons for the non-enablement rejection were discussed in detail in the office action mailed on 8/12/04. In response to Applicant's response regarding any knockout mouse has a well-established utility, the examiner does not agree with Applicant's assertion that the claimed invention has a well-established utility. Applicant is reminded that in MPEP, the guideline for the utility requirement clearly states: "An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible." A "well-known utility" is a specific, substantial and credible utility

which is well know, immediately apparent, or implied by the specification's disclosure of the properties of the material, alone or taken with the knowledge of one skilled in the art. Neither a "well-established utility" nor a "specific utility" applies to any utility that one can dream up for an invention or a utility that would apply to virtually every member of a general class of materials, such as proteins or DNA. (Paragraph bridging pg 32-33 of utility guidelines). In the instant case, the utility that applies to any knockout mouse is not specific to the claimed invention, the GPCR knockout mouse. Therefore, the claimed invention does not have a credible, substantial and specific utility.

In response to Applicant's argument of the commercial sale of the claimed mouse, Applicant is reminded that the sale of a product does not automatically gives the product patentable use according to the statue of 35 U.S.C.101 and the utility guideline set forth in the MPEP. Commercial success is only considered as secondary evidence for overcoming a 103 (a) rejection according to guidelines set by MPEP. If Applicant considers the sale of the claimed invention proves the utility and teaches specifically how to use the claimed invention, Applicant is invited to provide case law that validate such statement. Neither *Brenner v Manson* nor *Phillips Petroleum Co. v. U.S. Steel Corp.* supports the notion that commercial sale validates the patentably utility of a claimed invention.

The examiner's statement in the previous 103 rejection was directed to claims with different invention (targeting vectors and method of making a mouse) and scope, and this rejection became moot when the claims are cancelled or amended to the current scope. This statement cannot be relied on to demonstrate a patentable utility of the instant claimed invention because it merely provides a reason for making a GPCR targeting construct of entirely different

scope (without the limitation of the instantly claimed phenotype). It is well known to knock out a gene to determine its function or what will happen when the gene is not expressed. However, such scientific "utility" is not the same as "patentable utility" or a "well-established" utility. Applicant's assertion that the claimed mouse is useful to study the function of GPCR is an invitation for further research on the claimed invention in which the function of said invention Applicant clearly does not know.

The examiner cannot agree with Applicant's assertion that the claimed invention can be used to study GPCR's role in immunological disorders and anxiety, whereas a GPCR agonist would have value in control such process. The specification does not teach any phenotype of the claimed mouse that is relevant to anxiety. Furthermore, the specification fails to teach what type of immunological disorder the claimed mouse represents. Although the specification teaches that the claimed mouse exhibits cellular infiltration of lung, pancreas and liver tissues, it does not teach what type of immunological disorder such phenotype is related to. In addition, there is no nexus between the observed phenotype and the knockout GPCR gene because it is unclear whether the phenotype results directly from the deletion of the GPCR gene or from alteration of the genetic background that affects other gene pathways. As such, the specification fails to teach a credible, substantial and specific utility of the claimed mouse. Moreover, one skilled in the art would not know how to use a GPCR agonist for controlling the immunological disorder or anxiety because it is unclear how such agonist would function in such disorder.

In response to Applicant's argument regard *In re Brana*, the examiner does not agree that it applies in the instant case. Applicant has taken one conclusion out of the context. Although the case law states "Usefulness in patent law, and in particular in the context of pharmaceutical

inventions, necessarily includes the expectation of further research and development," it is referring to a chemical compound for its anti-tumor activity which has been demonstrated in tumor cell line. The specification of that application has taught a substantial and specific use for the claimed compound. However, in the instant case, the claimed knockout mouse does not have a specific and substantial use since the specification does not teach credibly what disease model the claimed mouse represents and/or what type of drug the claimed mouse can screen. As discussed above, the utility of studying the function of the GPCR is an invitation of further research in which the function of the claimed invention is not known. Moreover, using the mouse comprising null-reporter to study gene expression is not a patentable utility because it is not a substantial and specific utility for the instant claimed mouse, which is a transgenic mouse comprising GPCR null allele. Therefore, one skilled in the art would not know how to use the claimed invention according to the embodiments disclosed by the instant specification. The rejection is thus maintained.

In response to the 112 1st paragraph rejection, Applicant argues that there is no requirement that a claim to a novel composition recites a phenotype or property. Applicant further argues that there is no unpredictability in making and using the claimed invention, a mouse with a null allele of GPCR gene. Applicant cites Doetschmann and asserts that ablation of function is expected to result in the same phenotypic response. Lastly, Applicant asserts that the Crawley reference provides with guidance in behavioral genetics for one skilled in the art to make an informed choice of the best inbred strain for the development of a new null mutation, whereas the phenotypic analysis performed by Applicant were based on age, gender and strain

matched wild type controls, and already took any effect of strain variances into account. Applicant thus concludes that the claimed mouse is enabled by the instant specification.

These arguments These arguments have been fully considered but deemed unpersuasive. The reasons for non-enablement of the invention are discussed in detail in the office action mailed on 8/12/04. Applicant clearly misconstrues the examiner's position of the phenotype being the essential element of the claimed invention. Although there is no requirement for the claimed invention to recite a property or characteristic, the 112 1st statue requires the claimed invention to be described in a way to enable one skilled in the art to make and use the claimed invention without undue experimentation. Since the phenotype of the claimed mouse is unpredictable at the time the inventions was made, the claim must recite the phenotype of the claimed mouse because one skilled in the art would not know how to use a knockout mouse without any phenotype. Although making a mouse with a null allele by a replacement vector usually knockout the gene, the phenotype is still unpredictable because it not only depends on the function of the endogenous gene but also what exogenous DNA the gene is replaced with. Moreover, the product claims do not have the limitation of null allele being made by insertion of a positive selection marker. As such, the phenotype of the claimed mouse is unpredictable. For reasons discussed in the above regarding the lack of utility of the claimed mouse, one skilled in the art would not know how to use the GPCR knockout mouse. Although the claimed invention is a product claim, the specification needs to teach how to make and use the claimed product according to the embodiment disclosed in the specification. The specification discloses that the claimed mouse can be used to screen drugs and serve as disease model, however, one of skilled in the art would not known how to use such mouse model if it does not correlate with a human

disease. Applicant's assertion of using the mouse to study the function of the gene regardless of the phenotype is not a credible, specific and substantial use for reasons discussed above. Therefore, one skilled in the art still would not know how to use the claimed invention according to the teaching of the specification. Lastly, as acknowledged by Applicant, the Crawley reference discusses strains to strains variation in the art of making and testing the true phenotype of the transgenic knockout mouse, especially the strains C57BL/6 and 129, which is used to make the instant invention according to the specification. Although Applicant use gender, age and strain matched wild type controls, the phenotype of a mutant mouse is not only the result of the targeted gene, but it also reflects interactions with background gene, and other unknown mutations in the genetic background (see pages 107 last paragraph through page 108 1st paragraph). Since two strains commonly used in ES cell and knockout generation C57BL/6 and various substrains of 129 are unusual on many standard behavioral paradigms (see page 108, 2nd paragraph), further characterization is required to make sure that the claimed phenotype is truly resulted from the inhibition of the GPCR gene. Therefore, for reasons discussed in the previous office action and above, the claimed invention is not enabled.

Newly added claims 72-76 are rejected under 35 U.S.C 101/112 1st paragraph for same reasons set forth in the previous office action mailed on 8/12/04 and discussed above.

New Grounds of Rejection Necessitated by Applicant's Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

> pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 63-70 and 72-75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amended claims are drawn to a mouse whose genome comprises a null endogenous GPCR allele, wherein said allele comprises exogenous DNA the comprises a visible marker which is capable of expression in spleen. The original specification does not disclose a knockout mouse comprises a visible marker that is capable of expression in spleen. The disclosure of a single lacZ gene is not sufficient to support the claimed genus of "a visible marker gene that is capable of expression in skin." Therefore, such recitation constitutes new matter.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 70 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 70 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how to introduce exogenous DNA that comprises a visible marker into the transgenic mouse. The claim only recites introducing a targeting construct capable of disrupting the GPCR gene without mentioning a visible marker.

Claim Objections

Claim 76 is objected to as being dependent upon a cancelled base claim (1). Applicant is advised to rewrite the claim in independent form including all of the limitations of (canceled) base claim (1).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine X Qian Ph.D.
Examiner
Art Unit 1636

DAVE TRONG NGUYEN
PRIMARY EXAMINER